REMARKS

Claims 1-3 are pending. Claim 1 and 3 have been amended to recite proper antecedent basis. Support for this amendment is found in the Specification on page 58, lines 1-16. New Claims 4-10 have been added. Support for newly added Claims can be found throughout the Specification. Support for Claim 4 is found on page 19, lines 17-24. Support for Claim 5 is found on page 10, lines 8-15. Support for Claim 6 is found on page 12, lines 17-20 and page 27, lines 14-22. Support for Claim 7 is found on page 59, lines 19-22 and page 60, lines 7-24 and support for Claim 8 is found on page 16, lines 12-15. Support for Claims 9 and 10 is found on page 10, lines 16-21. The Specification has been amended to comply with the requirements to properly indicate trademarks and to update the status of a related application. No new matter is added. Entry of this amendment into the application is respectfully requested.

Rejection of Claims 2 and 3 under 35 U.S.C. § 112, Second Paragraph

Claims 2 and 3 are rejected under 35 U.S.C. § 112, Second Paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claims 1 and 3 have been amended to recite "TNF-mediated neurogenerative disease," thus providing proper antecedent basis. This amendment more clearly describes and distinctly claims the subject matter Applicants regard as the invention.

Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 1-3 under 35 U.S.C. § 103(a)

Claims 1-3 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Beck *et al.* (Acta Neurologica Scandinavica, 1988 Oct, Vol. 78, pp. 318-323) in view of the abstract of Beck *et al.* (Immunobiology, 1987, Vol. 175, pp. 91-92) and the abstract of Selmaj *et al.* (Neuroimmunology, 1987, Vol. 16, page 159).

The Examiner states "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to treat human multiple sclerosis by the administration of an anti-TNF alpha antibody... One of skill in the art would recognize that

binding to the anti-TNF antibody was effective at protecting mice from the pathological effects of cerebral malaria and therefore i[t] would be reasonable to conclude that anti-TNF antibodies would protect humans from the pathological effects of multiple sclerosis, because both multiple sclerosis and cerebral malaria are mediated by elevated levels of TNF alpha".

Applicants respectfully disagree. Applicants' invention relates to methods for treating TNF-mediated neurodegenerative diseases in a human, comprising administering at least one anti-TNF monoclonal antibody, or a TNF binding fragment thereof. In one embodiment, the antibody is a chimeric antibody comprising at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region. The Specification provides extensive details regarding producing the TNF-α antibodies and properties and characteristics (*e.g.*, specificity and affinity) of the antibodies useful for therapeutics.

The Beck *et al.* 1988 reference (*Acta Neurol. Scand.*, 78:318-323 (1988)) describes increased production of TNF preceding clinical manifestation in multiple sclerosis (MS). The Examiner asserts that because the effective use of neutralizing TNF antibodies providing protection from pathological effects was observed in mice susceptible to cerebral malaria, one of ordinary skill in the art would recognize the ability to protect humans from the pathological effects of multiple sclerosis.

Applicants respectfully disagree with this conclusion. First, Applicants' claims are directed to methods of treatment, not prevention or protection. Second, Applicants' claims are directed to neurodegenerative diseases such as MS, not malaria. The sole basis of the Examiner's conclusion is the weak correlation between the observation of elevated TNF levels in MS patients and the elevated TNF levels in cerebral malaria. No other parallels are drawn. Clearly, this lack of evidence does not justify the Examiner's conclusion. Anti-TNF antibodies, such as the monoclonal antibodies of Applicants' claimed invention and their use as therapeutics are not taught in this reference. The Beck *et al.* reference fails to disclose production of antibodies or any of the distinguishing characteristics of the antibody needed for therapy. The antibodies used in the cerebral malaria study are not described or characterized in the reference and, thus, no conclusion and expectation of success can be made for their use in MS treatment of humans.

The Beck *et al.* abstract describes an increase of TNF production paralleling exacerbation of MS. Additionally, there is a statement regarding ***in vitro*** neutralization with anti-TNF-α antibodies (see, first sentence, last paragraph). No description at all is given in either Beck reference as to how to produce or use TNF-α antibodies but for one line in the Beck 1988 reference that states "[t]he cytotoxic agent was completely neutralized by TNF-α antibodies, produced by repeated injection of recombinant TNF-α... (p. 320)" Both references are silent with regard to characteristics of the antibody such as specificity, type, and whether the antibody is a polyclonal or monoclonal. Additionally, no evidence or description is given regarding affinity. Not **all** antibodies generated to TNF-alpha will abrogate **all** effects of TNF-alpha. Without more description of the anti-TNF antibody, there can be no reasonable expectation of success that the TNF-α antibody described in the reference will have a therapeutic benefit *in vivo*.

The abstract of Selmaj *et al.* discloses that TNF mediates myelin damage in mouse cultures. However, the reference discloses that "the results *may suggest* that soluble factors are involved in demyelination *in situ* ... and that the TNF effect *may* involve an ion channel effect." (Emphasis added, last sentence). The reference also states that the TNF effect was not reversible. Again, no evidence is disclosed concerning the use of an antibody for neutralizing the speculative effect TNF has on the myelin sheath. Also, no teaching or suggestion of the effect an antibody to TNF-α may have on any of these speculative TNF effects is provided, let alone whether or not the effect of TNF or an antibody to TNF would be observed *in vivo* in a human.

In view of the above, the Examiner has failed to establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F. 2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Assuming, *arguendo*, that a *prima facie* case of obviousness does exist, objective evidence presented below overcomes the case of nonobviousness. Objective evidence of nonobviousness must be considered, as stated in the MPEP at § 2141:

> Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence.

The claimed invention has led to unexpected results in relation to the prior art, and has satisfied a long-felt need in the relevant field. The fact that others in the field had tried for years to achieve a result, yet had failed, is evidence that the invention would not have been obvious to those skilled in the art when it was invented.

The claimed methods utilize compounds that have been shown to have unexpected results in terms of the degree of success in clinical studies, particularly in studies involving patients with long-term refractory TNFα-mediated disease. *See* Elliott, M. J., *et al.*, "Treatment of Rheumatoid Arthritis with Chimeric Monoclonal Antibodies to Tumor Necrosis Factor α," *Arthritis Rheum, 36*:1681-1690 (1993) (Exhibit A) (hereinafter "Elliott"). The magnitude of these results in the treatment of a TNFα-mediated disease could not have been reasonably predicted from the prior art. As noted in Elliott on page 1688, due to multiple and overlapping effects of cytokines such as IL-1 and TNFα and the fact that cytokines induce production of other cytokines and of themselves, there had been pessimism about whether targeting a single cytokine *in vivo* would have any beneficial effect. See also, Trentham, D. M., "Immunotherapy and Other Novel Therapies," *Curr. Opin. Rheumatol., 3*:369-372, 370 (1991) (Exhibit B) ("...the relevance of tumor necrosis factor and the biological outcome of its banishment by a monospecific inhibitor remain in doubt..."); and *Id.* at 371 ("Unidimensional attacks on aberrant immune pathways might have a limited effect on the underlying disease process"). This initial skepticism as to the merits of the compounds used in the invention by experts in the field further establishes the nonobviousness of this invention. MPEP § 2141.

The cited references, whether considered alone or in combination, do not enable the

production of TNF-α antibodies for use in the methods claimed by Applicants. Without this teaching, the cited references clearly do not render the invention obvious. The references provide no basis for producing TNF-α neutralizing antibodies that can be used for *in vivo* therapeutic uses in humans. This deficiency can not be remedied by knowledge of one of skill in the art. Antibodies produced from TNF-α are likely to lack specificity and/or pharmaceutical stability. It is not readily apparent, upon studying the teachings of the references, that one would have a reasonable expectation of success to generate an antibody to TNF-α that meets the criteria needed to be useful in Applicants' methods without the detrimental stability problems. The references do not reasonably suggest that the unexpected and superior results achieved and described herein were possible. Moreover, the claimed invention has led to unexpected results and clearly satisfies a long felt but unsatisfied need. Thus, the cited references whether considered alone or in combination do not render Applicants' invention obvious. Withdrawal and reconsideration of the rejections are respectfully requested.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the IDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,
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Dated: April 14, 2004